

# IMPLEMENTATION AND ASSESSMENT

If the Action Plan for Liver Disease Research is to be successful, it will require effort for its implementation as well as active assessment of its success. The importance of these elements led to their inclusion in the initial structure and design of the Action Plan. The basis for implementation and assessment is that the Action Plan is not a final document but is rather an ongoing process with specific goals and benchmarks.

The organizational structure of the Action Plan has depended upon the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee (DDICC), and its implementation and assessment of progress will also be carried out using this mechanism, which enables trans-NIH and trans-agency coordination. Following the release of this Action Plan, the Liver Disease Subcommittee of the DDICC will meet annually to review the research goals identified in the Action Plan and to discuss both the implementation of efforts to address these goals, and the periodic assessment of progress toward reaching these goals over the next decade. These collaborations among NIH components and Federal agencies should work synergistically to minimize redundancy and maximize the research return on investments directed toward liver and biliary diseases. Efforts to carry out the Action Plan will also benefit from the leadership and focus of the Liver Disease Research Branch of the Division of Digestive Diseases and Nutrition of the NIDDK, NIH.

Table 1 provides cross-tabulation of how various NIH components could contribute to and collaborate on the implementation of strategies to address each of the 16 topic areas in liver and biliary diseases identified in this Action Plan. Through future meetings and communications, the Liver Disease Subcommittee of the DDICC will consider these potential contributions as well as steps to reach the Action Plan's specific research goals in the short-, intermediate-, and long-term, including those identified in the chapters of the Action Plan. Such steps include the organization of workshops, databases and tissue banks, program announcements and requests for applications, as well as establishment of networks of investigators. These approaches will help to develop the research tools and collaborative partnerships necessary to focus the research community's efforts on pursuing the research goals. Some of these steps would represent a continuation or expansion of existing efforts, while others would require the development of new investigator-initiated research directions and program initiatives through various means of NIH support.

Importantly, the 16 Working Groups will be asked to continue their involvement in the Action Plan and help in the active assessment of progress. In preparation for the annual overview of the Action Plan conducted by the Liver Disease Subcommittee of the DDICC, the chairpersons of each working group will be asked to assess progress towards each of the goals outlined in the matrices that follow the

chapters. The chairpersons will be assisted in this effort by the staff of the Liver Disease Research Branch, which will coordinate and conduct teleconferences with the members of the working group to prepare this assessment.

The 214 research goals outlined in the Matrix after each chapter will be used as guideposts by which to gauge progress toward meeting the overall aims of the Action Plan. These goals will be assessed in the annual meetings of the Liver Disease Subcommittee and will be specifically monitored by the Liver Disease Research Branch in coordination with the chairpersons of individual working groups involved in the assessment. In addition, benchmark goals that cover the wide range of research areas outlined in the 16 chapters and focus on measurable research goals that are important and cross-cutting will be developed and monitored.

An important timepoint in the implementation of the Action Plan will be the 5-year mark following its release. At this point, a formal meeting will be sponsored by the Liver Disease Research Branch which will include the 16 chairpersons of the working group, the Liver Disease Subcommittee of the DDICC, and relevant academic and advocacy groups. This open meeting will provide an in-depth analysis of progress toward meeting the goals of the Action Plan with input provided by the external research and advocacy community, many of whom participated in the development of the Action Plan. At this point, research progress and remaining opportunities related to the goals will be reviewed and approaches to remaining long-term research goals will be assessed. At this meeting, the DDICC would also consider how new scientific and epidemiologic developments, which will inevitably occur during the preceding 5-year period, call for modification of the Action Plan's research goals. A similar, open-forum analysis and reconsideration of research goals will be conducted at the close of the 10-year time period.

**Table 1. Potential Contributors to Efforts to Address Research Goals ^**

|         | Working Groups* |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |
|---------|-----------------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|
| NIH ICs | 1               | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| NCCAM   |                 | • |   | • | • |   | • | • |   |    |    |    | •  |    |    |    |
| NCI     | •               | • | • |   | • | • |   |   | • |    | •  |    |    | •  | •  | •  |
| NCMHD   |                 |   |   |   | • | • | • |   | • |    | •  |    |    | •  | •  |    |
| NCRR    |                 |   |   |   | • | • | • | • | • | •  | •  | •  | •  | •  | •  |    |
| NHGRI   | •               |   | • | • |   |   |   |   |   | •  | •  |    |    |    |    |    |
| NHLBI   | •               |   | • | • | • | • |   |   |   |    | •  |    | •  |    |    |    |
| NIAAA   |                 | • | • |   | • | • | • | • |   |    | •  |    |    | •  |    |    |
| NIAID   |                 | • | • |   | • | • | • | • | • | •  |    | •  |    | •  | •  | •  |
| NIBIB   |                 |   |   |   |   |   |   |   |   |    | •  | •  | •  | •  | •  | •  |
| NICHD   |                 |   | • | • |   |   | • |   | • | •  |    |    |    |    |    |    |
| NIDA    |                 | • | • |   | • | • |   |   |   |    |    |    | •  |    |    |    |
| NIDDK   | •               | • | • | • | • | • | • | • | • | •  | •  | •  | •  | •  | •  | •  |
| NIEHS   | •               | • | • | • |   |   | • | • |   |    |    |    |    | •  |    | •  |
| NIGMS   | •               | • | • | • |   |   |   | • |   |    |    |    |    |    |    |    |
| NINR    |                 |   |   |   |   | • |   |   |   | •  |    | •  | •  |    |    |    |
| OAR     |                 |   |   |   | • | • | • | • |   |    |    |    |    |    |    |    |
| ODS     | •               |   |   |   |   |   | • | • |   |    |    |    |    |    |    |    |
| ORD     |                 |   | • |   |   |   |   |   | • | •  | •  |    |    |    |    |    |
| ORWH    |                 |   |   |   |   |   | • |   | • |    |    |    |    |    |    |    |

ICs = Institutes, Centers, and Offices. See Appendix C for explanation of acronyms.

^ Potential contributors listed in this table have not necessarily committed to supporting these or other efforts at this point in time, but will consider this list during their review of the Action Plan and determine how they can best contribute to its implementation.

\* Working Groups for the Action Plan for Liver Disease Research:

- 1: Cell and Molecular Biology
- 2: Liver Injury, Inflammation, Repair, and Fibrosis
- 3: Developmental Biology and Regeneration
- 4: Bile, Bilirubin and Cholestasis
- 5: Viral Hepatitis
- 6: HIV and Liver Disease
- 7: Fatty Liver Disease
- 8: Drug- and Toxicant-Induced Liver Disease
- 9: Autoimmune Liver Disease
- 10: Pediatric Liver Disease
- 11: Genetic Liver Disease
- 12: Liver Transplantation
- 13: Complications of Liver Disease
- 14: Liver Cancer
- 15: Gallbladder and Biliary Disease
- 16: Liver Imaging and Biotechnology

# SUMMARY RECOMMENDATIONS

Liver and biliary diseases constitute a large number of conditions that affect people of all ages and all walks of life. Some of these diseases are common, such as fatty liver disease, hepatitis C, and gallstones; others are rare, such as biliary atresia, autoimmune hepatitis, and cholangiocarcinoma. Importantly, however, these diseases have major effects on the health and quality of life of persons who are affected by them. Furthermore, most liver and biliary diseases can be prevented and, if not prevented, most can be successfully treated. Without prevention or treatment, liver disease can lead to cirrhosis, end-stage liver disease, and liver failure. Once end-stage liver disease develops, the only means of reversing the disease and achieving long-term survival is liver transplantation.

This trans-NIH Action Plan for Liver Disease Research focuses upon means by which NIH-supported basic and clinical research can improve ways to prevent, diagnose, and treat liver disease. Importantly, significant advances in clinical management of liver disease will arise largely as a result of significant advances in basic research. In the last 10 to 20 years, major advances in biomedical research and remarkable new insights into basic biology and the pathobiology of disease have occurred. During this time, important new insights have been made into the structure and function of the liver and how it responds to injury and diseases. It is important to continue this growth in basic scientific discovery, but it is also important to rapidly translate the findings from basic research into clinical practice. This Action Plan is focused both on promoting basic research on liver biology and

disease and on actively translating findings from basic research into practical means of prevention and treatment of liver disease. This Action Plan outlines the major challenges in liver disease research, categorizing them into 16 topic areas as presented in 16 chapters. Each chapter provides a background to the area, a summary of recent important research advances, and a finite list of important research goals that are categorized in a 3-by-3 matrix based on whether they are short-, intermediate- or long-term and whether they are low-, medium- or high-risk, in terms of their difficulty of attainment. A total of 214 research goals were identified.

The goals for future NIH-supported research over the next decade identified in the 16 chapters of the Action Plan reveal several common themes as important priorities. Some of these common themes are further expanded in this summary. This list includes cross-cutting goals that were identified by several Working Groups as important in advancing liver and biliary research overall, as well as areas identified by individual Working Groups that are not likely to advance without additional research focus. These ten goals should not be considered the ten most important research goals, nor are they listed in priority order. Rather, these ten goals should be considered representative **benchmarks** by which to gauge the overall success of this Action Plan, in terms of objective progress in liver and biliary disease research over the next ten years.

### **One: Improve the success rate of therapy of hepatitis C.**

At present, antiviral therapy is successful in eradicating hepatitis C virus infection in approximately 50 percent of patients. Further advances are needed to **increase this response rate to greater than 90 percent** for patients infected with all genotypes and for therapy to be more effective in special populations (e.g., children, minority individuals, the elderly), as well as in persons with co-morbidities (e.g., HIV infection, renal disease, immune deficiencies, psychiatric and neurologic disease). These advances in therapy will come from the development of new antiviral agents and means of improving response rates to existing agents.

### **Two: Develop effective therapies that can be used in fatty liver disease, both alcoholic and nonalcoholic.**

At present, no specific therapies exist that have been shown to significantly impact alcoholic and nonalcoholic fatty liver disease. These diseases, however, are common and can lead to cirrhosis, end-stage liver disease, and liver failure. Advances in understanding the mechanisms of injury in nonalcoholic and alcoholic liver disease could be translated into therapies to reverse or impede the progression of these diseases. An important goal for research in the next 10 years is to **develop specific therapies for alcoholic and nonalcoholic fatty liver disease** that reverse or impede the progression of disease in at least half of patients.

### **Three: Develop regimens of antiviral therapy that are effective in long-term management of hepatitis B.**

Although an effective vaccine is available for hepatitis B, there are millions of individuals who already have chronic HBV infection accompanied by significant liver disease that can lead to cirrhosis or liver cancer. Several therapies have been approved for treatment of hepatitis B, but their long-term safety and efficacy have yet to be proven, and their relative and interactive roles have not been defined. In the next ten years, an important goal is to **define a practical regimen of therapy for chronic hepatitis B** that allows for mitigation of hepatocellular injury and reversal or prevention of disease progression in at least 90 percent of patients.

### **Four: Develop sensitive, specific, and noninvasive means of assessing disease stage (i.e., extent of fibrosis) in chronic liver disease.**

Further progress in treating liver disease is hampered by the difficulty in measuring disease progression. At present, hepatic fibrosis is considered the best indicator of disease stage because advanced fibrosis (cirrhosis) typically marks the final stage of chronic liver disease progression. However, currently, the only reliable means of assessing hepatic fibrosis is liver biopsy, which is an invasive and expensive procedure. The application of newer approaches to liver proteomics, gene expression, metabolomics, and imaging should demonstrate reliable noninvasive means of assessing severity and stage of disease. In the next ten years, an important goal is to **develop accurate and reliable means of assessing disease activity and hepatic fibrosis in a noninvasive manner** that would replace the need for liver biopsy to assess disease progression in clinical research studies and improve patient care.

**Five: Develop sensitive and specific means of screening individuals at high risk for early hepatocellular carcinoma.**

The major dreaded complication of chronic liver disease and cirrhosis is liver cancer, a highly fatal tumor that is difficult to diagnose and to treat. It is likely that treatments to limit fibrosis and disease progression will also help to prevent liver cancer. However, also needed are reliable (i.e., sensitive and specific) means of early diagnosis of liver cancer at a point when the tumor can be removed surgically or successfully treated with local ablative therapies or liver transplantation. **A simple and accurate biomarker for liver cancer** capable of detecting at least 80 percent of tumors at a point when they are smaller than 3 cm is an important goal for future research.

**Six: Develop means to prevent gallstones.**

Gallstones affect at least 12 percent of the adult population, and approximately 10 percent of Americans will, at some point in their lives, undergo cholecystectomy for treatment of gallstones. This makes gallbladder disease one of the major cost burdens on the U.S. health care system. The cause of gallstones is not well-defined, but recent research has provided new, exciting insights into their pathogenesis. A major goal for research in the next ten years is to translate these new findings into a **practical means of preventing gallstones** that can be applied to persons at high risk for developing gallstone disease.

**Seven: Elucidate the cause of biliary atresia.**

Biliary atresia is a rare disease, but it is the major reason for liver transplantation in children and leaves a child with a need for lifetime management of the liver transplant. The etiology of biliary atresia is unknown and advances in its management and prevention will require a major breakthrough in understanding the pathogenesis of this condition. An important goal for research in the next 10 years is to **elucidate the cause of biliary atresia** and, if possible, apply this knowledge to improve management or to prevent this disease.

**Eight: Improve the safety and define optimal use of living donor liver transplantation.**

The major challenges facing liver transplantation in the United States are: (1) to improve the ability of health care providers to offer liver transplantation through increasing the availability of organs while decreasing the overall need for transplantation by improving means to manage liver disease; and (2) to improve the outcome of transplantation, particularly long-term health outcomes and quality of life in recipients. Currently, the most promising means of increasing the availability of livers for transplantation is the use of living donor liver transplantation. However, a significant concern with using organs from living donors is the safety of the operation for the donor and the outcome of the transplant in the recipient. A major goal for liver disease-related research for the next ten years is to **improve the safety and outcome of living donor liver transplantation** for both donors and recipients.

**Nine: Develop standardized and objective diagnostic criteria of major liver diseases and their grading and staging.**

There is considerable variation in diagnostic terms, criteria for diagnosis, means of assessment, and grading and staging systems currently used for liver disease. Standardization of nomenclature, diagnostic criteria, and instruments for assessing liver disease are essential for clinical research. For example, standardization of nomenclature, grading and staging systems for hepatitis C has enabled important comparisons between studies of natural history and therapy done throughout the world. These systems have become essential in assessing the efficacy of new therapies and are widely used in academic investigation, industry-supported clinical research, decision making by regulatory agencies, and even clinical practice. The whole field of liver disease would benefit from more rigorous application of nomenclature, diagnostic terms, diagnostic criteria, standardization of laboratory test assessment, grading systems to assess severity or activity of disease, and staging systems to assess stage and progression of disease. An important goal for the next ten years is to ***develop widely accepted and standardized nomenclature, diagnostic criteria, means of assessment, and grading and staging systems for the major liver and biliary diseases.***

**Ten: Decrease the mortality rate from liver disease.**

The age-adjusted death rate from liver disease has been stable during the last 10 years. While rates of death from chronic liver disease and cirrhosis have been declining, deaths from viral hepatitis and liver cancer have been increasing, such that the overall mortality rate from liver disease is largely unchanged. With improved means of prevention and treatment of liver diseases, these rates should decrease. An important goal in the next ten years is to achieve a ***decrease of at least 20 percent in the age-adjusted death rates from liver disease in the United States.***

This trans-NIH Action Plan lays out the challenges to the liver disease research community for the next ten years and should help to bring about advances in diagnosis, prevention, and treatment of liver diseases that will materially affect a large proportion of the American population.